Local and In-Transit Metastases Following Definitive Excision for Primary Cutaneous Malignant Melanoma

DANIEL F. ROSES, M.D.,* MATTHEW N. HARRIS, M.D.,* DARRELL RIGEL, M.D.,† ZEV CARREY, M.D.,† ROBERT FRIEDMAN, M.D.,† ALFRED W. KOPF, M.D.†

A total of 672 consecutive patients with clinical stage I and stage II primary cutaneous malignant melanoma were treated by excision of 3.0 to 5.0 cm of surrounding skin down to and including the underlying fascia when the lesion exceeded 0.5 mm thickness (Breslow measurement). More conservative margins were taken in locations where such excisions would result in significant cosmetic or functional morbidity and for thinner lesions (<0.5 mm). Seven of 658 patients with clinical stage I disease (1.1%) and three of 14 patients with clinical stage II disease (21.4%) developed histologically verified local metastases within 5 cm of the primary excision scar or skin graft. Fifteen patients wth stage I disease developed in-transit metastases (2.3%) at a site more than 5.0 cm proximal to the surgical scar or skin graft but not beyond the regional nodal group. Two patients with stage II disease who had developed local metastases also developed in-transit metastases (14.3%). No patient with a lesion less than 1.0 mm thick has had a local recurrence. Nine of the ten patients (90%) who developed local metastases and 12 of the 17 patients (70.6%) who developed in-transit metastases have also developed systemic metastases to date. Local and in-transit metastases following such definitive excision is a significant indicator of disseminated systemic metastatic melanoma.

From the Division of Oncology, Department of Surgery and the Oncology Section, Skin and Cancer Unit, Department of Dermatology, New York University Medical Center, New York, New York

THE MOST ESSENTIAL ELEMENT in the treatment of a primary cutaneous malignant melanoma is adequate definitive excision. Numerous investigators have noted that removal of only the grossly apparent tumor risks local reappearance.[5,9,15] Therefore, excision with margins of histologically normal skin beyond the perimeter of the lesion has been recommended. The breadth and depth of such excisions, however, remains a source of controversy.[3,4,7] This is due in part to the tenuous justification for "wide and deep" excisions, based on observations in selected patients with locally advanced or widely disseminated malignant melanoma.[11,14] In addition, many surgical dictates on the margins of resection were proposed before the adoption of histopathologic methods of classifying primary cutaneous malignant melanomas.[5,17,22] Thus, the study of resection margins prior to these advances has been based on a broad spectrum of lesions, not taking into account the varied locations, thicknesses, and potential for metastases of the malignant melanomas under investigation.

In an attempt to assess the appropriateness of a uniform approach to definitive excision, a consecutive series of patients with clinical stage I and clinical stage II primary cutaneous malignant melanoma was studied. In each instance, the thickness of the primary malignant melanoma was measured by the Breslow method.[2]

Materials and Methods

A total of 672 patients treated at the New York University Medical Center for primary cutaneous malignant melanoma was studied. There were 658 patients with clinical stage I disease and 14 patients with clinical stage II disease (Table 1). Of the 658 patients with clinical stage I disease, 90 patients (14.0%) had their lesion on the skin of the head and neck region, 249 (37.7%) on the trunk, 148 (22.0%) on the upper extremity, 167 (25.2%) on the lower extremity and four (0.6%) on the perineum. Of the 14 patients with clinical stage II disease, five patients (20.0%) had their lesion on the skin of the head and neck region, three (33.3%) on the trunk, one (16.7%) on the upper extremity, and five (30.0%) on the lower extremity. The mean follow-up time for all patients included in this study was 44.8 months. The principles of treatment included a biopsy of the primary lesion in toto where feasible, so that step sections of the neoplasm could be reviewed microscopically. Thickness was measured by the technique of Breslow.[2] Where size and cosmetic considerations made this impractical, an appropriate incisional biopsy of a part of the lesion was

* Department of Surgery.
† Department of Dermatology.
Reprint requests: Daniel F. Roses, M.D., 530 First Avenue, New York, NY 10016.
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TABLE 1. *Thickness and Incidence of Local and In-Transit Metastases (n = 672)*

Thickness of Lesion in mm	Stage I Disease—All Cases		Stage I Disease with Local Metastases		Stage I Disease with In-Transit Metastases		Stage II Disease—All Cases		Stage II Disease with Local and/or In-Transit Metastases	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
0.00–0.50	115	(17.5)	0	(0.0)	0	(0.0)	0	(0)	0	(0.0)
0.51–1.00	192	(29.2)	0	(0.0)	1	(6.9)	0	(0)	0	(0.0)
1.01–1.50	115	(17.5)	1	(14.3)	4	(26.7)	2	(14.3)	0	(0.0)
1.51–2.00	71	(10.8)	0	(0.0)	2	(13.3)	1	(7.1)	0	(0.0)
2.01–2.50	40	(6.1)	0	(0.0)	0	(0.0)	1	(7.1)	1	(33.3)
2.51–3.00	33	(5.0)	1	(14.3)	1	(6.7)	2	(14.3)	0	(0.0)
3.01–3.50	24	(3.6)	1	(14.3)	2	(13.3)	1	(7.1)	0	(0.0)
3.51–4.00	17	(2.6)	1	(14.3)	1	(6.7)	1	(7.1)	0	(0.0)
4.01–4.50	15	(2.3)	1	(14.3)	2	(13.3)	2	(14.3)	2	(66.7)
4.51–5.00	12	(1.8)	2	(28.6)	1	(6.7)	0	(0.0)	0	(0.0)
>5.00	24	(3.6)	0	(0.0)	1	(6.7)	4	(28.6)	0	(0.0)
Total	658	(100)	7	(100)	15	(100)	14	(100)	3	(100)

performed to assess the area of presumably greatest thickness. In such instances, after definitive excision, it was ascertained if any non-biopsied area of the primary lesion had a greater thickness and, if so, this became the thickness of record. The margins of all definitive excision specimens were evaluated histologically as free of melanoma.

Treatment was individualized based upon the thickness of the primary neoplasm. Elliptical excisions were performed in most instances in order to achieve a primary closure whenever possible or to reduce the surgical defect and thereby minimize the size of the skin graft required. The excision margin with such elliptical excisions was considered the minimum distance of normal skin from the perimeter of the lesion or biopsy scar to the edge of the definitive resection. For lesions that were *in situ* and less than 0.5 mm in thickness, margins of at least 1.0 cm or more beyond the clinically visible perimeter of the lesion or scar from the original biopsy were maintained, provided that such excisions did not result in the sacrifice of a major structure, such as an eye. Primary closure usually was achieved, with the rare exception of lesions located in areas where there was minimal plasticity of the surrounding skin. In such situations, a small skin graft was required. For thicker lesions, wider excisions were performed. If the lesion was between 0.5 and 1.0 mm, in thickness, minimum margins of 3.0 cm were obtained and, in most instances, a primary closure was achieved. For lesions thicker than 1.0 mm, minimum margins of 3.0 to 5.0 cm were obtained when feasible. When present, the underlying fascia was included in the surgical specimen and skin grafts were applied when needed. Skin grafts were required for closure in 66.3% (242/365) of patients treated for lesions of 1.0 mm or greater thickness. In most instances, the width of excision between 3.0 and 5.0 cm was determined by the location of the tumor. For most lesions on the trunk and thigh, for example, 5.0-cm minimum margins were maintained. For lesions on the forearm and leg as well as the hands, feet, and scalp, the minimum margins more frequently approached 3.0 cm. For lesions exceeding 0.5 mm in thickness on the face, cosmetic considerations frequently led to a reduction in margins to 2.0 to 3.0 cm. Partial resections of ears were performed to obtain at least 2.0-cm margins. Lesions of the digits were treated by excision and skin grafting for *in situ* lesions and amputation for invasive lesions. For toes, ray amputations usually were performed. For the thumb, amputation was at the metacarpalphalangeal joint. The index and small fingers were amputated at the proximal metacarpal joint, while for middle and ring fingers, a portion of the proximal phalanx was preserved when possible.

Elective regional lymph node dissections were performed in 49.5% (326/658) of the stage I patients. These were done for lesions where the route of lymphatic drainage was predictable or where the excision of the primary lesion overlay the regional nodal group if there were no contraindicating medical conditions.[18,19,20] In addition, early in the series, elective regional nodal dissections were performed for lesions of 0.75 mm or greater thickness, but more recently, they have been performed only for patients with lesions of 1.0 mm or greater thickness.[21]

Local metastasis was defined as biopsy-proven metastatic disease within a distance of 5.0 cm from the perimeter of the primary closure scar or skin graft. In-transit metastasis was defined as biopsy-proven metastatic disease at a site more than 5.0 cm proximal to the scar or skin graft but not beyond the regional lymph nodes. Five-year local recurrence rates were calculated by a Kaplan-Meier survival analysis.[13]

TABLE 2. *Time from Development of Local and In-Transit Metastases to Clinically Defined Systemic Metastases (n = 25)*

Classification	n	No. (%) Who Developed Systemic Disease n (%)	Time Range until Systemic Disease (Months)	Average Time until Systemic Disease (Months)
Stage I with local metastases	7	6 (85.7)	0–23	9.7
Stage I with in-transit metastases	15	10 (66.7)	0–18	4.7
Stage II with local and/or in-transit metastases	3	3 (100)	0–10	3.3

Results

Of the 658 patients with clinical stage I disease, seven patients (1.1%) developed local metastases. The life table adjusted local recurrence rate at 5 years was 1.8%. Of the seven local metastases, three developed within 6 months, one within 7 months, one within 14 months, one within 37 months, and one within 64 months after initial surgical therapy. The thicknesses of these lesions are noted in Table 1. Of the 658 patients, 15 patients (2.3%) developed in-transit metastases.

No patient with a primary tumor of less than 1.0 mm in thickness developed local metastases, although one patient with a lesion that was 0.82 mm thick did develop in-transit metastases. Five patients with lesions 1.0 to 1.5 mm thick did develop local or in-transit metastases following definitive surgery for the primary lesion. Of the 15 patients with in-transit metastases who entered the study as clinical stage I, three patients had histologically diagnosed metastases to regional lymph nodes draining the primary site.

Of the 14 clinical stage II patients, three patients (21.4%) developed local metastases. Two of these three patients also developed in-transit metastases. Neither of these patients had their primary cutaneous malignant melanoma on an extremity.

Of the seven patients with clinical stage I primary cutaneous malignant melanoma who developed local metastases, six patients developed disseminated systemic metastatic melanoma. Evidence of systemic metastases developed concurrently with local metastases in three patients, and at varying times thereafter up to 23 months from the diagnosis of the local metastatic disease in the three additional patients. The average time to appearance of systemic metastases from the diagnosis of local metastases was 9.7 months. Of the three patients with clinical stage II malignant melanoma who developed local metastases, all developed systemic malignant melanoma, either concurrent with the diagnosis of local disease or up to 10 months thereafter. Of the 17 patients who developed in-transit metastases, 12 patients have developed disseminated systemic metastatic melanoma to date (Table 2).

In patients with lesions of 1.0-mm thickness or greater, the incidence of in-transit metastases for those in clinical stage I undergoing elective regional node dissection with no histologically demonstrated nodal metastases was 12/282 (4.3%), 2/44 (4.5%) for those in clinical stage I undergoing elective regional node dissections and having histologically demonstrated nodal micrometastases, and 2/14 (14%) for those in clinical stage II with histologically verified nodal metastases.

Discussion

An early concept in determining the operative approach to malignant melanoma in this century was set forth by Handley[11] in his Hunterian Lectures of 1907 entitled "The Pathology of Melanotic Growths in Relation to their Operative Treatment." He vigorously endorsed the view, based chiefly upon a single necropsy of a patient who died with widespread metastatic disease, that the process of dissemination from a malignant melanoma was primarily one of centrifugal lymphatic permeation. A circular incision was advised "around the tumor at what was judged by present standards to be a safe and practicable distance."

A second concept in the development of current principles for excision of a primary cutaneous malignant melanoma was that malignancy developed not only from the focal transformation of a few cells, but also from neoplastic changes involving an area of skin larger than the visible neoplasm. Wong,[24] in a study of 12 cases of malignant melanoma, found that in seven, there were increased numbers of melanocytes up to 5.0 cm from the edge of the lesion. Some of these showed bizarre morphologic appearances. Cochran[6] also noted "field change" in the melanocytes around primary malignant melanomas. Inherent in both foregoing concepts concerning the local growth of malignant melanoma, as it relates to surgical therapy, was the possibility that embolic malignant melanoma within regional lymphatics or occult foci of residual neoplastic cells might act as a source for subsequent local or distant metastases. More recently, however, Day et al.[7] have suggested that the width of surgical resection margins may have no effect on survival, even for high-risk malignant melanomas.

In evaluating any surgical treatment of primary malignant melanomas, the most significant determinant of efficacy must be the incidence of local recurrences.

These have been reported to range from 50%, as quoted by Cade,[5] to 20% to 30%, reported by Pack,[15] to 18%, reported by Petersen et al.,[15] to 8% to 12%, reported by Watson.[22] Wilson[23] found the local reappearance rate following wide excision to be 3.4%, as opposed to excisional biopsy alone, which resulted in a local reappearance rate of 57.1%. Petersen et al.,[16] in studying 19 patients with recurrence of malignant melanoma in the skin near the original lesion, found that eight recurrences were under the graft, whereas in 11 patients, they were within 10 cm from the edge of the primary excision. In eight patients, the recurrence was within 5 cm of the original excision, with the remaining recurrences within 15 cm, all in the direction of the regional lymphatics. Milton[11] studied 65 patients with advanced disease and found 47 with recurrences at sites that could have been removed at the time of initial surgery. Of the 47 local recurrences, 16 recurrences first appeared in the scar, whereas 13 were in-transit between the primary tumor site and the lymph nodes. These observations suggest that local recurrences are often the first sites of metastatic disease and that excision beyond the grossly visible neoplasm is necessary to decrease their occurrence. While the survival of patients who have lesions that have already metastasized widely will not be changed by wide excision of the primary site, measures taken to reduce local recurrences with their potentially significant morbidity is an appropriate goal for the surgeon in the treatment of malignant melanoma. A consensus has not been reached, however, as to the extent of excision needed in order to achieve optimal control locally. Numerous investigators have advocated excisions ranging anywhere from just beyond the visible tumor to 5.0 cm of normal skin.[7,9,14,16] What has been lacking in the studies reported to date is a uniform prospective treatment plan to allow evaluation of results for lesions with accurately defined thicknesses.

We feel that the low incidence of local recurrence in our experience supports a policy of treatment based on accurate histopathologic evaluation of the primary tumor, excisions with conservative margins for thin lesions, and more extensive margins for thicker lesions tempered by cosmetic and functional considerations where significant. The occurrence of local metastases appears to be greatly dependent on the thickness of the primary tumor when first treated. This assessment requires an appropriate biopsy of the lesion *in toto* or *in parte* of the thickest area and step-sectioned histopathologic evaluation.[17] No patient in our series has developed local metastases with a lesion less than 1.0 mm thick, although one patient has developed in-transit metastases with a lesion 0.82 mm in thickness. Certainly, excisions with margins exceeding 3.0 cm would seem unjustified for such thin lesions. However, even a conservative excision may require skin graft closure in some locations, while in others, excisions with margins of 3.0 cm may often be closed primarily.

Breslow and Macht[3] studied a series of 62 patients who had cutaneous malignant melanomas measuring less than 0.76 mm in thickness. Such lesions were excised with margins of as little as 1.0 mm up to 3.0 cms or more. All of the patients survived free of disease over 5 years and none had local metastases. The authors concluded that malignant melanomas less than 0.76 mm in thickness could be treated by conservative excision with primary closure. While we have excised such thin lesions more conservatively than thicker lesions, we have attempted to obtain a wide excision if commensurate with a primary closure in such instances. It must also be pointed out that there may be potential dangers in the conservative local excision of lesions that have had less than optimal biopsies, so that interpretation of histologic material does not allow an accurate assessment of thickness. In this setting, a conservative excision might be performed for a lesion with greater metastatic potential than can be appreciated on the inadequate biopsy specimen. Likewise, significant areas of regression in a primary malignant melanoma may belie the potential of the primary tumor to metastasize both locally and widely and must be weighed carefully in decisions regarding excision margins. Gromet et al.[10] have reported a substantial rate of metastases in thin melanomas that had histologic evidence of regression.

Cascinelli et al.[4] noted local metastases as a first sign of relapse of the disease in 25 of 593 patients (4.2%) with stage I malignant melanomas. The per cent of recurrence increased from 1.1 to 5.8 with increasing thickness and decreased from 10.8 to 3.0 with increasing margins of resection. In evaluating the results, the authors considered resection margins by five groups with 1.0-cm increments and tumor thickness by increments of 1.0 mm. They found that while survival did not seem to be related to resection margins, local recurrences, when evaluated by width of excision and maximum thickness, were decreased with increasing margins of resection. The trend to decreasing local recurrence was demonstrated as margins went from 1.0 cm to 5.0 cm.

In a study by Bockelbrink et al.,[1] of 588 patients with high-risk primary stage I cutaneous malignant melanoma, it was concluded that the rate of distant metastases was independent of the width of surgical excision. However, a higher incidence of local recurrence was noted for an excision smaller than 30 mm, although this did not appear to influence the overall prognosis.

A flexible surgical policy that allows wider excisions for more invasive thicker lesions is appropriate in our

view. The low rate of local metastases in our experience leads us to consider more conservative excisions for all primary malignant melanomas as being potentially hazardous. While the main barrier to successful treatment for malignant melanoma has been failure to prevent or eradicate hematogenously disseminated disease that is present at the time of initial definitive therapy, the difficulties encountered in the management of locally metastatic disease and the disability that such local reappearance may cause the patient encourages us to continue our present treatment plan. The development of systemic metastases in nine of ten patients (90%) with local metastases and 12 of 17 patients (70.6%) with in-transit metastases indicates that for the majority of patients, regional recurrence after such definitive excision connotes more widespread disease.

It has been suggested that the occurrence of in-transit metastases may be potentiated by lymphatic stagnation that might ensue between the primary site of a malignant melanoma and the regional lymph node basin as a result of lymphadenectomy.[8,13] The low incidence of in-transit metastases in clinical stage I patients undergoing lymphadenectomy (4.3%) with lesions of 1.0-mm or greater thickness does not suggest that node dissection contributes to the occurrence of such regional recurrence. This is particularly so since patients with lesions of 1.0-mm or greater thickness in clinical stage I who had proven micrometastases had an almost identical incidence of in-transit metastases (4.5%). If stagnation of intervening lymphatics, contaminated with melanoma between the primary site and the nodal drainage basin, is a major contributor to the occurrence of in-transit metastases, then the expected incidence in the latter group might be higher.

While a randomized study to evaluate prospectively differing approaches to width and depth of excision would be required to provide more definitive answers on the extent of excision required in the local control of a malignant melanoma, the wide range of possible excision margins, the extreme variability of thicknesses of the primary neoplasms and of prognosis in various body locations, and the resection constraints posed by vital structures suggests that an extraordinarily large number of patients would be required in order to arrive at reliable conclusions. If such a study could be done, it is probable that multiple dominant factors would emerge that could predict the highest rate of local cure achievable for a particular malignant melanoma with the least extensive surgical procedure.

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